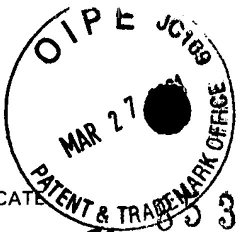

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Docket No: 2094/1E285-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kevin M. GORMAN, David R. PATTERSON, Jeffrey M. LINNEN and Keming SONG

Serial No.: 09/494,332 Art Unit: 1655

Filed: January 28, 2000 Examiner: J. GOLDBERG

For: OLIGONUCLEOTIDE PRIMERS FOR EFFICIENT MULTIPLEX DETECTION OF HEPATITIS C VIRUS (HCV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND METHOS OF USE THEREOF

RESPONSE TO OFFICE ACTION AND AMENDMENT UNDER 37 C.F.R. § 1.111

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Office Action mailed on December 14, 2000 in connection with the above-captioned patent application and in accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks. These amendments are made pursuant to the requirements of Rule 121. Accordingly, Applicants are submitting herewith: (1) a copy of the amended

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paragraphs and claims marked up, as required under 37 C.F.R. § 1.121(b)(1)(iii) and § 1.121(c)(ii), to show all changes relative to the previous version of each claim and attached hereto as Exhibit A. Applicants also submit herewith:

(2) a Petition for Extension of Time for a period of **one month** (from **March 14, 2001** up to and including **April 12, 2001**), accompanied by the appropriate fee;

(3) an Amendment Fee Transmittal, accompanied by the appropriate fee;

(4) a Transmittal of Substitute Sequence Listing;

(5) a Substitute Sequence Listing, in paper and computer readable forms; and

(6) a Supplemental Information Disclosure Statement, accompanied by the appropriate fee and including Form PTO-1449 with copies of the references cited therein.

It is believed that no additional fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is required or that any refund is due, the Commissioner is authorized to charge the required fee(s) and/or credit the refund(s) due to Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE SPECIFICATION:

Enter the following new paragraph on page 1, line 1 of the specification as originally filed:

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This application claims benefit, under 35 U.S.C. § 119(a) to United States Provisional Application Serial No. 60/118,498 filed on February 3, 1999.

Amend the paragraph at lines 18-26 on page 15 of the specification, as indicated in the accompanying Exhibit A, to read as follows:

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The sample is then subjected to reverse transcription using (a) random primers, such as random hexamer primers obtained from Pharmacia Biotech, Piscataway, NJ, and/or (b) primers derived from the 5' or 3' non-coding regions of the HCV RNA genomic sequence. Reverse transcription is carried out using conventional procedures, such as are described in *Current Protocols in Molecular Biology*, Volumes I, II, and III, 1997 (F.M. Ausubel ed.); in U.S. Patent No. 5,322,770; in Young, et al., *J. Clin. Microbiol.* 31(4):882 (1993); Myers et al., *Biochemistry* 30(3):7661 (1991); or as described in provisional patent application Serial No. 60/118,520, filed February 3, 1999.

IN THE CLAIMS:

Please amend claims 1, 10, 16, 25 and 31, as indicated in the attached Exhibit A, and add new claims 43-46 so that the pending claims will be as follows:

1. (Amended) A method for detecting Hepatitis C Virus (HCV) RNA or Human Immunodeficiency Virus (HIV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using RNA derived from said sample as a template and at least one reverse transcription primer that will prime reverse transcription of DNA from HCV RNA and at least one reverse transcription primer that will prime reverse transcription of DNA from HIV RNA to produce reverse transcription products comprising (a) HCV-specific reverse transcription products, (b) HIV-specific reverse transcription products, or (c) a combination of (a) and (b);

(B) amplifying said reverse-transcription products using one or more pairs of oligonucleotide primers specific for the 5' noncoding region of HCV and one or more pairs of oligonucleotide primers specific for HIV to produce amplification products comprising (a) HCV-specific amplification products, (b) HIV-specific amplification products, or (c) a combination of (a) and (b);

wherein each of said pairs of oligonucleotide primers specific for HCV comprises:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 1>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 2>;

wherein each of the pairs of oligonucleotide primers specific for HIV-1 comprises a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>,

wherein each of the pairs of oligonucleotide primers specific for HIV-2 comprises a forward primer with the sequence 5'-GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence 5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>; and

(C) detecting said amplification products;

wherein detection of HCV-specific amplification products indicates the presence of HCV RNA in said sample, detection of HIV-specific amplification products indicates the presence of HIV RNA in said sample, and the detection of HCV-specific amplification products and HIV-specific amplification products indicates the presence of HCV RNA and HIV RNA in said sample.

2. A method as defined in claim 1, wherein said reverse transcription reaction is performed using random oligonucleotide primers.

3. A method as defined in claim 1, wherein said reverse transcription reaction is performed using one or more oligonucleotide primers having sequences corresponding to sequences in HCV RNA and one or more oligonucleotide primers having sequences corresponding to sequences in HIV RNA.

B1 cont

4. A method as defined in claim 1, wherein said amplifying is performed by a method selected from the group consisting of polymerase chain reaction, ligase chain reaction, strand displacement amplification, nucleic acid single base amplification, and transcription mediated amplification.

5. A method as defined in claim 1, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

6. A method as defined in claim 1, wherein said detecting comprises capturing said amplification products on a solid support containing (a) one or more HCV-specific oligonucleotide probes, (b) one or more HIV-specific oligonucleotide probes, or (c) a combination of (a) and (b) and quantifying said captured products using a colorimetric assay.

7. A method as defined in claim 6, wherein said HCV-specific probe consists of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> and said HIV-specific probe is selected from the group consisting of:

(a) 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>;

(b) 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>; and

(c) 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

8. A method as defined in claim 1, wherein said sample is selected from the group consisting of blood, serum, plasma, urine, saliva, and cerebrospinal fluid.

9. A method as defined in claim 1, wherein said co-detecting is simultaneous.

10. (Amended) A method for amplifying Hepatitis C Virus (HCV) DNA or Human Immunodeficiency Virus (HIV) DNA, said method comprising:

(A) performing a polymerase chain reaction on a DNA sample suspected to contain HCV DNA, HIV DNA, or a combination of HCV DNA and HIV DNA, using one or

more pairs of oligonucleotide primers specific for the 5' noncoding region of HCV and one or more pairs of oligonucleotide primers specific for HIV to produce amplification products comprising (a) HCV-specific amplification products, (b) HIV-specific amplification products, or (c) a combination of (a) and (b);

wherein each of said pairs of oligonucleotide primers specific for HCV comprises:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 1>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 2>;

wherein each of the pairs of oligonucleotide primers specific for HIV-1 comprises a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>; and

wherein each of the pairs of oligonucleotide primers specific for HIV-2 comprises a forward primer with the sequence 5'-

GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence 5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>.

11. A method as defined in claim 10, further comprising:

(B) detecting said amplification products,

wherein detection of HCV-specific amplification products indicates the presence of HCV DNA in said sample, detection of HIV-specific amplification products indicates the presence of HIV DNA in said sample, and the detection of HCV-specific amplification products and HIV-specific amplification products indicates the presence of HCV DNA and HIV DNA in said sample.

B1 Cont

12. A method as defined in claim 11, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

13. A method as defined in claim 11, wherein said detecting comprises capturing said amplification products on a solid support containing (a) one or more HCV-specific oligonucleotide probes, (b) one or more HIV-specific oligonucleotide probes, or (c) a combination of (a) and (b) and quantifying said captured products using a colorimetric assay.

14. A method as defined in claim 13, wherein said HCV-specific probe consists of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> and said HIV-specific probe is selected from the group consisting of:

(a) 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>;

(b) 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>; and

(c) 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

B1 cont

15. A method as defined in claim 1, wherein said co-amplifying is simultaneous.

16. (Amended) A method for detecting Hepatitis C Virus (HCV) RNA or Human Immunodeficiency Virus (HIV) RNA in a biological sample, said method comprising:

Sub C2

(A) performing a reverse transcription reaction using RNA derived from said sample and internal positive control (IPC) RNA as a template, at least one reverse transcription primer that will prime reverse transcription of DNA from IPC RNA, at least one reverse transcription primer that will prime reverse transcription of DNA from HCV RNA, and at least one reverse transcription primer that will prime reverse transcription

of DNA from HIV RNA to produce reverse transcription products comprising (a) IPC-specific reverse transcription products and (b) HCV-specific reverse transcription products, (c) HIV-specific reverse transcription products, or (d) any combination of any of the foregoing;

(B) amplifying said reverse-transcription products using one or more pairs of oligonucleotide primers specific for IPC, one or more pairs of oligonucleotide primers specific for the 5' noncoding region of HCV, and one or more pairs of oligonucleotide primers specific for HIV to produce amplification products comprising (a) IPC-specific amplification products (b) IPC-specific amplification products and HCV-specific amplification products, (c) IPC-specific amplification products and HIV-specific amplification products, or (d) a combination of any of the foregoing;

wherein each of said pairs of oligonucleotide primers specific for IPC comprises:

(1) forward primer 5'-CGCCAGCGTGGACCATCAAGTAGTAA-3' (IPCF1) <SEQ ID NO. 8>, and

(2) reverse primer 5'-CACGATCCTGGAGCAGACACTGAAGA-3' (IPCR1) <SEQ ID NO. 9>;

wherein each of said pairs of oligonucleotide primers specific for HCV comprises:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 10>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 11>; and

wherein each of the pairs of oligonucleotide primers specific for HIV-1 comprises a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>,

wherein each of the pairs of oligonucleotide primers specific for HIV-2 comprises a forward primer with the sequence 5'-GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence 5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>; and

(C) detecting said amplification products

wherein detection of IPC-specific amplification products indicates the presence of IPC RNA in said sample, detection of HCV-specific amplification products indicates the presence of HCV RNA in said sample, detection of HIV-specific amplification products indicates the presence of HIV RNA in said sample, and the

detection of HCV-specific amplification products and HIV-specific amplification products indicates the presence of HCV RNA and HIV RNA in said sample.

17. A method as defined in claim 16, wherein said reverse transcription reaction is performed using random oligonucleotide primers.

18. A method as defined in claim 16, wherein said reverse transcription reaction is performed using one or more oligonucleotide primers having sequences corresponding to sequences in IPC RNA, one or more oligonucleotide primers having sequences corresponding to sequences in HCV RNA and one or more oligonucleotide primers having sequences corresponding to sequences in HIV RNA.

19. A method as defined in claim 16, wherein said amplifying is performed by a method selected from the group consisting of polymerase chain reaction, ligase chain reaction, strand displacement amplification, and transcription mediated amplification.

20. A method as defined in claim 16, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

21. A method as defined in claim 16, wherein said detecting comprises capturing said amplification products on a solid support containing (a) one or more IPC-specific oligonucleotide probes, (b) one or more HCV-specific oligonucleotide probes, (c) one or more HIV-specific oligonucleotide probes, or (d) a combination of any of (a), (b), and (c) and quantifying said captured products using a colorimetric assay.

B1 cont

22. A method as defined in claim 21, wherein said IPC-specific probe consists of 5'-CTGCGTTAGACCGAGAACTGTGGATAAAGG-3' <SEQ ID NO. 17>, said HCV-specific probe consists of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> and said HIV-specific probe is selected from the group consisting of:

(a) 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>;

(b) 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>; and

(c) 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

23. A method as defined in claim 16, wherein said sample is selected from the group consisting of blood, serum, plasma, urine, saliva, and cerebrospinal fluid.

24. A method as defined in claim 16, wherein said co-detecting is simultaneous.

25. (Amended) A method for amplifying Internal Positive Control (IPC) DNA, Hepatitis C Virus (HCV) DNA, or Human Immunodeficiency Virus (HCV) DNA, said method comprising:

(A) performing a polymerase chain reaction on a DNA sample containing IPC DNA and suspected to contain HCV DNA, HIV DNA, or any combination of any of the foregoing, using one or more pairs of oligonucleotide primers specific for IPC, one or more pairs of oligonucleotide primers specific for the 5' noncoding region of HCV, and one or more pairs of oligonucleotide primers specific for HIV to produce amplification products comprising (a) IPC amplification products, (b) IPC amplification products and HCV-specific amplification products, (c) IPC amplification products and HIV-specific amplification products, or (d) a combination of any of (a), (b), and (c);

wherein each of said pairs of oligonucleotide primers specific for IPC comprises:

(i) forward primer 5'-CGCCAGCGTGGACCATCAAGTAGTAA-3' (IPCF1) <SEQ ID NO. 8>, and

(ii) reverse primer 5'-CACGATCCTGGAGCAGACACTGAAGA-3' (IPCR1) <SEQ ID NO. 9>;

wherein each of said pairs of oligonucleotide primers specific for HCV comprises:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 10>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 11>; and

wherein each of the pairs of oligonucleotide primers specific for HIV-1 comprises a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>,

wherein each of the pairs of oligonucleotide primers specific for HIV-2 comprises a forward primer with the sequence 5'-GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence 5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>.

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26. A method as defined in claim 10, further comprising:

(B) detecting said amplification products,

wherein detection of IPC-specific amplification products indicates the presence of IPC DNA in said sample, detection of HCV-specific amplification products indicates the presence of HCV DNA in said sample, detection of HIV-specific amplification products indicates the presence of HIV DNA in said sample, and the detection of HCV-specific amplification products and HIV-specific amplification products indicates the presence of HCV DNA and HIV DNA in said sample.

27. A method as defined in claim 26, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

28. A method as defined in claim 26, wherein said detecting comprises capturing said amplification products on a solid support containing (a) one or more IPC-specific oligonucleotide probes, (b) one or more HCV-specific oligonucleotide probes, (c) one or more HIV-specific oligonucleotide probes, or (d) any combination of any of the foregoing and quantifying said captured products using a colorimetric assay.

29. A method as defined in claim 28, wherein said IPC-specific probe consists of 5'-CTGCGTTAGACCGAGAACTGTGGATAAAGG-3' <SEQ ID NO. 17>, said HCV-specific probe consists of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-

27-PRB) <SEQ ID NO. 12> and said HIV-specific probe is selected from the group consisting of:

(a) 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>;

(b) 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>; and

(c) 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

30. A method as defined in claim 29, wherein said co-amplifying is simultaneous.

31. (Amended) A kit suitable for co-detecting HCV RNA and HIV RNA in a biological sample, said kit comprising:

(a) a pair of oligonucleotide primers specific for the 5' noncoding region of HCV comprising:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 10>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 11>; and

(b) oligonucleotide primers specific for HIV-1 which comprise a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>,and a pair of oligonucleotide primers specific for HIV-2 which comprise a forward primer with the sequence 5'-GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence:

5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>.

32. A kit as defined in claim 31, further comprising a pair of oligonucleotide primers specific for IPC, wherein said pair of oligonucleotide primers specific for IPC comprises forward primer 5'-CGCCAGCGTGGACCATCAAGTAGTAA-3' (IPCF1) <SEQ ID NO. 8> and reverse primer 5'-CACGATCCTGGAGCAGACACTGAAGA-3' (IPCR1) <SEQ ID NO. 9>.

33. A kit as defined in claim 31, further comprising one or more probes.

34. A kit as defined in claim 32, further comprising one or more probes.

35. A kit as defined in claim 33, wherein said probes are selected from the group consisting of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>, 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>, 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>, and 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

36. A kit as defined in claim 34, wherein said IPC-specific probe consists of 5'-CTGCGTTAGACCGAGAACTGTGGATAAAGG-3' (IPC1P) <SEQ ID NO. 17>, said HCV-specific probe consists of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>, and said HIV-specific probe is selected from the group consisting of:

(a) 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>;

(b) 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>; and

(c) 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

37. A kit for co-amplifying HCV DNA and HIV DNA in a DNA sample, said kit comprising:

(a) a pair of oligonucleotide primers specific for the 5' noncoding region of HCV comprising:

(i) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 10>, and

(ii) reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 11>;

(b) oligonucleotide primers specific for HIV-1 which comprise a forward primer with the sequence:

5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3' (JBLTR4) <SEQ ID NO. 3>, and a reverse primer specific for HIV-1 selected from the group consisting of:

(1) 5'-GGGTCTGAGGGATCTCTAGTTACC AGAGT-3' (JBLTR6) <SEQ ID NO. 4>, and

(2) 5'-TGTTCGGGCGCCACTGCTAGAGA-3' (JBLTR8) <SEQ ID NO. 5>,and a pair of oligonucleotide primers specific for HIV-2 which comprise a forward primer with the sequence 5'-GGGAGGTTCTCTCCAGCACTAGCA-3' (2LTRe) <SEQ ID NO. 6>, and a reverse primer specific for HIV-2 with the sequence:

5'-GCGACTAGGAGAGATGGGAACACACA-3' (2LTR-R1) <SEQ ID NO. 7>.

38. A kit as defined in claim 37, further comprising a pair of oligonucleotide primers specific for IPC, wherein said pair of oligonucleotide primers specific for IPC comprises forward primer 5'-CGCCAGCGTGGACCATCAAGTAGTAA-3' (IPCF1) <SEQ ID NO. 8> and reverse primer 5'-CACGATCCTGGAGCAGACACTGAAGA-3' (IPCR1) <SEQ ID NO. 9>.

39. A kit as defined in claim 37, further comprising one or more probes.

40. A kit as defined in claim 38, further comprising one or more probes.

41. A kit as defined in claim 39, wherein said probes are selected from the group consisting of 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>, 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>, 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>, and 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

42. A kit as defined in claim 40, wherein said IPC-specific probe consists of 5'-CTGCGTTAGACCGAGAACTGTGGATAAAGG-3' (IPC1P) <SEQ ID NO. 17>, said HCV-specific probe consists of 5'-CCTTTCGCGACCCAACACTACTCGGCT-

3' (C252-27-PRB) <SEQ ID NO. 12>, and said HIV-specific probe is selected from the group consisting of:

(a) 5'-CAACAGACGGGCACACACTACT-3' (JBLTRpr3) <SEQ ID NO. 13>;

(b) 5'-GAACAGATGGGCACACACTGCT-3' (JBLTRpr4) <SEQ ID NO. 16>; and

(c) 5'-CCACGCTTGCTTGCTTAAAGACCTC-3' (2LTRpr1) <SEQ ID NO. 14>.

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43. (New) A method according to claim 1 wherein HCV RNA and HIV RNA are co-detected in the sample by detecting:

(i) HCV-specific amplification products; and

(ii) HIV-specific amplification products.

44. (New) A method according to claim 10 wherein HCV DNA and HIV DNA are co-amplified.

45. (New) A method according to claim 16, wherein HCV RNA and HIV RNA are co-detected in the sample by detecting:

(i) HCV-specific amplification products; and

(ii) HIV-specific amplification products.

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46. (New) A method according to claim 25 wherein the IPC DNA, HCV DNA and HIV DNA are co-amplified.

REMARKS

Claims 1-42 are pending in this patent application. Claims 1, 10, 16, 25 and 31 have been amended, and new dependent claims 43-46 have been added. Thus, claims 1-46 will be pending upon entry of this amendment.

Claims 1, 10, 16 and 25 have been amended solely to clarify the claim language. In particular, these claims have been amended to more particularly point out that HCV nucleic acids, HIV nucleic acids, or both may be amplified and/or detected using the recited methods. New dependent claims 43-46 have been added to distinctly claim particular embodiments of the claimed methods in which *both* HCV *and* HIV nucleic acids are amplified and/or detected. The amendments are fully supported in the application as originally filed and do not constitute new matter. For support, the Examiner's attention is respectfully directed, *e.g.*, to page 2, lines 26-28; page 4, lines 15-17; page 10, lines 14-15; page 11, lines 17-19; page 11, lines 23-25; page 16, lines 7-9; and the original claims of the application as filed.

The specification has also been amended. In particular, a new sentence has been added at the beginning of the specification, pursuant to 37 C.F.R. § 1.78, to include a specific reference to the prior provisional application. Upon review of the specification, Applicants have also noticed that page 15 of the application includes a

reference to a provisional patent application that is identified by its attorney docket number (*i.e.*, attorney docket number 2094/0E287). The serial number for this provisional patent application, which was not available when this specification was first filed, is now available. Accordingly, the paragraph has been amended to incorporate that serial number (*i.e.*, Serial Number 60/118,520).

The above-made amendments do not, therefore, contain new matter. Entry of the amendments into the file history of this application and consideration of these remarks is respectfully requested.

<u>THE EXAMINER'S OBJECTIONS TO THE SPECIFICATION HAVE BEEN OBVIATED</u>

The Examiner's objections to the specification for this application have been duly noted. In particular, the Examiner has objected to the specification because the first sentence does not contain a specific reference to the provisional application to which priority is claimed (*i.e.*, Serial No. 60/118,498, filed February 3, 1999). Accordingly, a new sentence has been added at the beginning of this application to include a specific reference to the prior provisional application.

Applicants also acknowledge that SEQ ID NOS:1 and 10 of this application are identical, as noted by the Examiner. The Examiner has also noticed that SEQ ID NO:2, as set forth in the Sequence Listing for this application, is identical to SEQ ID NO:11 except for one additional nucleic acid residue. Here, Applicants

respectfully point out that SEQ ID NOS:2 and 11, as recited in the pending claims, actually refer to the same nucleotide sequence:

5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294T25)

For example, the Examiner's attention is respectfully invited to the nucleotide sequence recited in claim 1(B)(ii) and in claim 16(B)(ii). Applicants submit herewith a Substitute Sequence Listing that corrects the nucleotide sequence set forth as SEQ ID NO:11. In particular, the nucleotide sequence set forth as SEQ ID NO:11 in the Substitute Sequence Listing is identical to the nucleotide sequence set forth as SEQ ID NO:11, *e.g.*, in claim 16(B)(ii).

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-42 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner contends that, the independent claims are directed to a method for detecting both HCV and HIV nucleic acids, but that the claims as pending may be directed to employing only HCV or HIV. The Examiner maintains that this language is confusing.

At the outset, Applicants respectfully submit that the claim language as originally written is not confusing and is fully definite under the meaning of 35 U.S.C. § 112, second paragraph. In particular, a skilled artisan will readily appreciate that the claimed methods and kits of this invention may be used to test simultaneously for the presence of HCV and/or HIV nucleic acids in a single sample, such as a clinical sample

from a patient who may be infected with either HCV, HIV or both HCV and HIV. Although the claimed methods test simultaneously for both HCV and HIV , upon completing the steps recited in the claims, either HCV nucleic acids, HIV nucleic acids or both may be amplified and/or detected, thereby indicating which type(s) of nucleic acid is(are) present in the sample. These metes and bounds are consistent with other diagnostic assays used in the art, and will be readily appreciated by the skilled artisan.

Nevertheless, Applicants have amended the independent claims in order to be fully responsive to this rejection and to expedite allowance of the application. In particular, claims 1, 10, 16 and 25 have been amended to particularly recite methods for amplifying and/or detecting HCV *or* HIV nucleic acids. Thus, the preamble of the claims, as amended, clearly points out that the claimed methods may be used to detect HCV nucleic acids, HIV nucleic acids, or both HCV and HIV nucleic acids. New dependent claims 43-46 recite preferred, non-limiting embodiments of the claimed methods where *both* HCV *and* HIV nucleic acids are detected in a single sample.

Finally, independent claim 31 has also been amended to particularly recite kits that are "suitable for" co-detecting HCV and HIV nucleic acids. Thus, the skilled artisan will readily appreciate that, while the claimed kits may be used in assays that detect both HCV and HIV nucleic acids, use of such kits is not limited to instances where nucleic acids from both viruses are detected in the same sample.

For all of the above reasons, Applicants submit that the rejection of claims under 35 U.S.C. § 112, second paragraph, has been obviated and that the rejection should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

The pending claims of this application have also been rejected under 35 U.S.C. § 103(a) as obvious over various references cited in the Office Action. In particular, the claims have been rejected as follows:

(1) Claims 1 and 3-15 have been rejected as obvious over Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han") and U.S. Patent No. 6,001,558 issued December 14, 1999 to Backus *et al.* ("Backus"), in view of Nedjar *et al.*, "Co-Amplification of Specific Sequences of HCV and HIV-1 Genomes by Using the Polymerase Chain Reaction Assay: A Potential Tool for the Simultaneous Detection of HCV and HIV-1", *J. or Virological Methods* 1991, 35:297-304 ("Nedjar");

(2) Claim 2 is rejected as obvious over Han and Backus in further view of Nedjar, and further in view of U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens"); and

(3) Claims 31, 33, 35, 37, 39 and 41 have been rejected as obvious over Han and Backus in view of Nedjar, and further in view of Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investment", *The Scientist* 1995, 9(15):20 ("Ahern")[1].

Each of these rejections is discussed in turn below.

A. *The legal standard for obviousness under 35 U.S.C. § 103(a):*

Three basic criteria must be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach all of the claimed limitations. The motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See, M.P.E.P § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Obviousness can only be established by combining or modifying the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. M.P.E.P. § 2143.01. See also, *In re Fine*,

[1] This reference has been cited in the Office Action by the internet web page: www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998.

837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USQP2d 1941 (Fed. Cir. 1992). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990).

Here, the relevant inquiry is whether, at the time this application was filed, one of ordinary skill in the art would be motivated to modify and/or combine the teachings in the above-cited references. If one skilled in the art would have been so motivated, it must also be shown that the modification or combination would teach or suggest *every* element of the claimed invention so that the invention, as a whole, would be apparent to the ordinarily skilled artisan. M.P.E.P. § 2143.03. The invention must be apparent with a reasonable expectation of success. M.P.E.P. § 2143.02. Thus, modification and/or combination of the above-cited references must render the particular oligonucleotide sequences recited in the claims apparent to the skilled artisan. Moreover, it must also be readily apparent that the particular oligonucleotide sequences may be used, with a reasonable expectation of success, in a single assay capable of detecting *both* HCV *and* HIV nucleic acids.

The initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. In particular, the cited references must expressly or impliedly suggest the claimed invention, or the Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed

invention to have been obvious in light of the teachings of the references. M.P.E.P. § 2142; citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

As explained in detail below, the present Office Action does not satisfy these requirements and therefore fails to establish a *prima facie* case for obviousness. None of the references cited in the Office Action, either alone or in combination, provides or suggests the oligonucleotide sequence used in this invention; particularly the sequences used to amplify and/or detect HCV. Given only the references cited in by the Examiner and without the teachings of this application, a skilled artisan could not know *a priori* that any of the particular oligonucleotides recited in the pending claims could successfully amplify and/or detect HCV nucleic acids. Moreover, a skilled artisan would have no reasonable expectation that the recited oligonucleotides could be used successfully to either co-amplify or co-detect both HCV and HIV nucleic acids in a single assay. The rejections for obviousness should therefore be withdrawn.

B. The combined teachings of Han, Backus and/or Nedjar do not render the claimed invention obvious:

Claims 1 and 3-15 have been rejected as obvious over Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han") and U.S. Patent No. 5,001,558 issued December 14, 1999 to Backus *et al.* ("Backus") in view of Nedjar *et al.*, "Co-amplification of Specific Sequences of HCV and HIV-1 Genomes by Using the

Polymerase Chain Reaction Assay: a Potential Tool for the Simultaneous Detection of HCV and HIV-1" *J. of Virological Methods* 1991, 35:297-304 ("Nedjar"). In particular, Han allegedly teaches a genomic sequence from the 5' untranslated region (UTR) of the hepatitis C virus (HCV). According to the Office Action, Han further teaches that this sequence is highly conserved among viral isolates, and suggests that the sequence might be used as an HCV-specific probe. The Office Action therefore indicates that Han renders the HCV specific oligonucleotides of this invention obvious to one skilled in the art. However, the Han reference does not provide oligonucleotide sequences for any particular probe or primer, let alone the particular HCV specific oligonucleotide sequences of this invention.

Backus allegedly teaches a PCR assay for amplifying human immuno deficiency virus (HIV) that uses some oligonucleotides recited in the pending claims, and Nedjar allegedly teaches a PCR assay that co-amplifies and detects both HCV and HIV. The Examiner therefore concludes that, given these teachings, the particular co-amplification and co-detection assays of this invention would be obvious to one of ordinary skill in the art.

In response, Applicants submit that the particular HCV-specific oligonucleotide probes and primers of this invention would not have been obvious to one skilled in the art given only the teachings of the above-cited references. As such, the skilled artisan could not reasonably expect that these oligonucleotides could be used to successfully amplify and/or detect HCV nucleic acids. Moreover, the skilled

artisan could not know *a priori* that the HIV-specific oligonucleotide sequences recited in the claims could be used successfully in combination with the HCV-specific oligonucleotides of this invention.

To demonstrate this point, Applicants respectfully direct the Examiner's attention to Chapter 15.1, "Enzymatic Amplification of DNA by PCR: Standard Procedures and Optimization" from Ausubel *et al.* (Eds.), *Current Protocols in Molecular Biology*, Vol. 3 (John Wiley & Sons, 1998) pages 15.1.1-15.1.15 ("Ausubel"), which is cited in the accompanying Supplemental Information Disclosure Statement.[2] This reference specifically teaches that primer selection for PCR assays is:

> "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work."

See, in particular, page 15.1.7, left hand column under the heading "Primer Selection".

Next, Applicants invite the Examiner's attention to the reference by Elnifro *et al.*, "Multiplex PCR: Optimization and Application in Diagnostic Virology" *Clinical Microbiology Reviews* 2000, 13:559-570 ("Elnifro").[3] Elnifro reviews theoretical and practical bases of developing and optimizing multiplex PCR (*i.e.*, a variant of PCR in which more than one target sequence may be amplified; see the left hand column on

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[2] The Ausubel reference is cited as Reference No. 1 in Form PTO-1449 accompanying the Supplemental Information Disclosure Statement, and a copy of the Ausubel reference is submitted therewith.

[3] Elnifro is cited in Form PTO-1449 of the accompanying Supplemental Information Disclosure Statement as Reference No. 2. A copy of the reference is also submitted with the Form PTO-1449.

page 559 of Elnifro), particularly with respect to applications in diagnostic virology.

Elnifro notes in particular that:

> [t]he optimization of multiplex PCRs can pose several difficulties, including poor sensitivity or specificity and/or preferential amplifcation of certain specific targets. The presence of more than one primer pair in the multiplex PCR increases that chance of obtaining spurious amplification products, primarily because of the formation of primer dimers."

See, in particular, the last paragraph in the right hand column on page 559 of Elnifro.

Elnifro then goes on to state that:

> [e]mpirical testing and a trail-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design.

See, Elnifro at lines 1-6 of the left hand column on page 560.

Thus, at the time this application was filed the art of multiplex PCR optimization was unpredictable at best. In particular and as taught in the Ausubel reference discussed above, a skilled artisan could not know *a priori* whether a particular set of primers would successfully amplify a nucleic acid. Moreover, the Elnifro reference makes it clear that even if a particular primer pair is known to amplify a target nucleic acid when used alone (*i.e.*, in the absence of other primer pairs), there is no way to tell, except by trial-and-error, whether that primer pair may be used with other primers (*e.g.*, in a multiplex type PCR reaction, to amplify or detect more than one target nucleic acid).

Given all of these teachings, the particular probes and primers recited in the pending claims of this invention cannot be obvious over Han. Neither Han, nor any of the other references cited in the Office Action teaches or suggests the HCV-specific probes and primers of this invention. Nor can these HCV-specific probes or primers be obvious over Han. At best, given what is taught by Han a skilled artisan might only be motivated to try various probes and primer derived from the 5'-UTR taught in that reference, and to try amplifying and/or detecting HCV nucleic acids using these various primers. Obvious to try, however, is not that standard for obviousness under 35 U.S.C. § 103(a). "Both the suggestion and the expectation of success must be found in the prior art, not in Applicant's disclosure". *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Given Ausubel's teaching that selection of PCR primers is unpredictable, a skilled artisan could not have expected the particular probes and primers of this invention to successfully amplify and/or detect HCV nucleic acids.

The other references cited in the Office Action do not overcome any of the deficiencies of Han. Backus merely relates to the co-amplification and detection of HIV. Although the assays described by Backus may use certain oligonucleotide sequences that are also recited in the pending claims, the reference does not teach or suggest *any* oligonucleotide sequence for amplifying or detecting HCV nucleic acids, let alone the particular HCV-specific oligonucleotides of this invention. Moreover, Backus does not teach or suggest that the HIV-specific oligonucleotides mentioned therein may be used, *e.g.*, in a co-amplification or co-detection assay with *any* other oligonucleotide, let alone

the other oligonucleotides recited in the pending claims. Given what is taught by Elnifro, the use of Bakcus's HIV-specific nucleic acids in such a mutliplex type PCR reaction cannot, therefore, be obvious.

Nedjar describes a multiplex type PCR assay for co-amplifying HCV and HIV. However, this assay uses completely different oligonucleotide primers to amplify and detect target sequences from the two viruses. However, Nedjar does not teach or suggest the HIV-specific oligonucleotides recited in the pending claims. Thus, Nedjar can, at best, only motivate a skilled artisan to try a mutliplex type PCR assay using the HIV-specific oligonucleotides taught by Backus. However, the above-discussed teachings of Elnifro make it clear that a skilled artisan could not have any reasonable expectation of success when trying such a co-amplification or co-detection assay. In addition, Nedjar does not teach or suggest the HCV-specific oligonucleotides of this invention. Therefore, a mutliplex type PCR assay using those HCV-specific nucleic acids cannot be obvious in view of Nedjar or any other cited reference.

In conclusion, the teachings of Han, Backus and/or Nedjar, when consider alone or in combination, cannot render Applicants' claimed invention obvious. The obviousness rejection over these references should therefore be withdrawn.

C. *The Maertens patent does not overcome the deficiencies of the Han, Backus and Nedjar references:*

Claim 2 has been rejected under 35 U.S.C. § 103(a) as being obvious over Han and Backus in view of Nedjar, and in further view of U.S. Patent No.

5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens"). The Han, Backus and Nedjar references have been discussed in detail, *supra*. In particular and as discussed above, these references do not teach or suggest any of the HCV-specific oligonucleotide specific sequences of this invention. In addition, the references fail to teach the combined use of these or any other HCV-specific oligonucleotides in combination with the HIV-specific probes and primers recited in the pending claims.

Maertens allegedly teaches a method of genotyping HCV isolates using probes targeting sequences from the 5'-UTR of HCV and, in particular, using random primers. However, Maertens does not overcome any of the above-discussed deficiencies in the other cited references. In particular, Maertens does not teach or suggest any of the particular nucleic acid probes and primers of this invention.. Moreover, Maertens does not teach the combined use of any HCV-specific oligonucleotide in combination of HIV-specific probes or primers; *e.g.*, for a co-amplification or co-detection assay.

A *prima facie* case of obviousness requires that _all_ of the claimed limitations be found in the prior art. See, M.P.E.P. § 2143.03. As explained above, however, none of the cited references teaches or suggests the particular HCV-specific probes and/or primers of this invention. Moreover, the references do not teach or suggest usage of the HIV-specific oligonucleotide sequences recited in the pending claims in a co-amplification or co-detection assay with any HCV-specific sequence, let alone the particular HCV-specific sequences of this invention. Accordingly, the pending

claims are not obvious over Han, Backus or Nedjar when considered either alone, or in combination with each other and/or Maertens.

D. *The Ahern references does not overcome the deficiencies of the Han, Backus and Nedjar references:*

Claims 31, 33, 35, 37, 39 and 41 have been rejected under 35 U.S.C. § 103(a) as being obvious over Han and Backus in view of Nedjar, and further in view of Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investment", *The Scientist* 1995, 9(15):20 ("Ahern"). The references of Han, Backus and Nedjar have been discussed in detail, *supra*, and in connection with the other obviousness rejections.

Ahern does not overcome any of the deficiencies discussed above for the other references. Instead, Ahern merely teaches the general advantage of prepackaged kits of biological reagents. However, Ahern does not teach or suggest a PCR kit for co-amplifying HCV and HIV nucleic acids, let alone a kit containing the particular oligonucleotides of this invention. Accordingly, the invention is not obvious over the references cited in the Office Action, either alone or in view of Ahern.

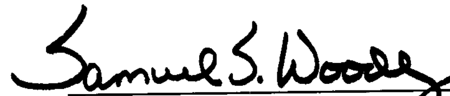
Applicants submit that each of the rejections under 35 U.S.C. § 103(a) has been obviated by the above remarks. In particular and as explained in detail above, none of the rejections satisfies the requirements necessary to establish a *prima*

facie case for obviousness under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that all of the rejections for obviousness be withedrawn.

CONCLUSION

For the reasons stated above, Applicants believe that the pending claims of this application, as amended, are in condition for allowance. Accordingly, withdrawal of all objections and rejections and reconsideration of the application are respectfully requested. The Examiner is invited to contact Applicants' representative at the below-indicated telephone number if (s)he believes it would advance prosecution of the application. An allowance is earnestly sought.

Respectfully submitted,



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